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EXAMINER
KUBELIK, ANNE R

ART UNIT	PAPER NUMBER
2638	12

DATE MAILED: 03/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/923,844	BAO ET AL.	
	Examiner	Art Unit	
	Anne R. Kubelik	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) *1-14, 23 and 27-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-22 and 24-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☒ The proposed drawing correction filed on *27 December 2002* is: a)☒ approved b)☐ disapproved by the Examiner

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8,9* .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

1. Applicant's election without traverse of Group II (claims 15-22 and 24-26) and SEQ ID NO:3 in Paper No. 11, filed 27 December 2002, is acknowledged. The restriction is made FINAL.

2. Claims 1-14, 23 and 27-34 are withdrawn from consideration as being drawn to nonelected inventions. A complete reply to the final rejection must include cancellation of nonelected claims and sequences or other appropriate action (37 CFR 1.144). See MPEP § 821.01. Claims 15-22 and 24-26 are examined to the extent they read on SEQ ID NO:3.

3. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825.

Applicant has filed proposed drawing changes that include sequence identifiers in the legends of Figures 4 and 5. In response to this action, Applicant is required to either submit corrected drawings **OR** amend the Brief Description of the Drawings for those figures.

Full compliance with the sequence rules is required in response to this Office action. A complete response to this Office action must include both compliance with the sequence rules and a response to the issues set forth below. Failure to fully comply with both of these requirements in the time period set forth in this Office action will be held to be non-responsive.

4. The abstract is not descriptive of the instant invention, which is a lipid transfer protein-encoding nucleic acid from sunflower, constructs and vectors comprising the nucleic acids, cells, plants and seeds comprising the constructs, and methods of using the constructs to create or enhance disease resistance in a plant. A new abstract is required that is clearly indicative of the

invention to which the claims are directed. The abstract of the disclosure should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

5. The title of the invention is not descriptive of the instant invention, as above. A new title is required that is clearly indicative of the invention to which the claims are directed. Note that titles can be up to 500 characters long.

6. The disclosure is objected to because it contains embedded hyperlinks and/or other forms of browser-executable code. See pg 13, lines 18-19. Applicant is required to delete the embedded hyperlinks and/or other forms of browser-executable code. See MPEP § 608.01.

Claim Objections

7. Claims 15 and 25 are objected to because they contain non-elected sequences.

8. Claim 16 is objected to because of the following informalities: there is an improper article before "nucleotide" in line 1.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 15-22 and 24-26 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one skilled in

the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are broadly drawn to lipid transfer protein-encoding nucleic acids with 70% identity to SEQ ID NO:3, nucleic acids comprising at least 16 contiguous nucleotides of a nucleic acid that encodes SEQ ID NO:4, or nucleic acids that hybridize to the latter nucleic acid. The claims are also drawn to constructs and vectors comprising the nucleic acids, cells, plants and seeds comprising the constructs, and methods of using the constructs to create or enhance disease resistance in a plant.

The instant specification, however, only provides guidance for isolation of lipid transfer protein (LTP) cDNA by sequencing cDNAs of RNAs expressed in sunflower in response to *Sclerotinia* infection and by isolating full-length cDNAs by RACE-PCR (example 1); and isolation of the LTP promoter by PCR (example 1). The cDNA is SEQ ID NO:3, which encodes SEQ ID NO:4; the promoter is SEQ ID NO:6. The specification also provides guidance for Northern analysis showing that LTP transcripts were induced by *Sclerotinia* infection (examples 2 and 3); and general guidance for transformation of sunflower and maize with a construct comprising SEQ ID NO:3 (examples 4 and 5).

The instant specification fails to provide guidance for lipid transfer protein-encoding nucleic acids with 70% identity to SEQ ID NO:3, nucleic acids comprising at least 16 contiguous nucleotides of a nucleic acid that encodes SEQ ID NO:4, or nucleic acids that hybridize to the latter nucleic acid.

The instant specification fails to provide guidance for construction or isolation of the claims nucleic acids. For example, the specification fails to provide guidance for the exact

hybridization or amplification conditions and probes/primers to use in isolation of nucleic acids other than SEQ ID NO:3.

The specification on pg 23, lines 4-18, suggests making variant nucleic acids by making conservative substitutions in the encoded protein. However, making such "conservative" substitutions (*e.g.*, substituting one polar amino acid for another, or one acidic one for another) does not produce predictable results. Lazar et al (1988, Mol. Cell. Biol. 8:1247-1252) showed that the "conservative" substitution of glutamic acid for aspartic acid at position 47 reduced biological function of transforming growth factor alpha while "nonconservative" substitutions with alanine or asparagine had no effect (abstract). Similarly, Hill et al (1998, Biochem. Biophys. Res. Comm. 244:573-577) teach that when three histidines that are maintained in ADP-glucose pyrophosphorylase across several species are substituted with the "nonconservative" amino acid glutamine, there is little effect on enzyme activity, while the substitution of one of those histidines with the "conservative" amino acid arginine drastically reduced enzyme activity (see Table 1). All these mutated proteins, however, would have at least 95% identity to the original protein and the nucleic acids encoding all these mutated proteins would hybridize under high stringency to the nucleic acids encoding the original protein.

It is not clear that the instant nucleic acid actually encodes an LTP involved in the defense reaction. The instant specification states that SEQ ID NO:4 has only 28-47% identity to lipid transfer proteins (pg 58, lines 4-12). The specification provides no evidence that SEQ ID NO:3 actually encodes a protein with lipid transfer protein activity. Duggleby (1997, Gene 190:245-249) teaches that "the function of any DNA sequence, whose identity is based solely on

homology, can only be proven by experiments designed to evaluate that function" (pg 248, left column, paragraph 4).

Additionally, it is noted that a search of GenBank found no sequences in either the nucleotide or protein databases that matched the GenBank Accession Numbers listed on pg 58, lines 4-12 of the specification, so a comparison between SEQ ID NO:4 and those sequences could not be made.

Lastly, not all nucleic acids that comprise 16 contiguous nucleotides of a nucleic acid that encodes SEQ ID NO:4 are lipid transfer proteins. Kragh et al (WO 95/11306) teach isolated nucleic acids encoding 21 contiguous nucleotides of a nucleic acid that encodes SEQ ID NO:4; these proteins are anti-fungal proteins, which function differently than LTPs (pg 8, paragraph 3).

The specification does not teach how to use a nucleic acid that does not encode a lipid transfer protein.

Given the claim breath, unpredictability, and lack of guidance as discussed above, undue experimentation would have been required by one skilled in the art to develop and evaluate lipid transfer protein-encoding nucleic acids with 70% identity to SEQ ID NO:3. Making all possible single amino acid substitutions (thus, substitutions of no more than three nucleotides) in an 97 amino acid long protein like that encoded by SEQ ID NO:3 would require making and analyzing 19^{97} nucleic acids; these nucleic acids would have at least 98.9% identity to SEQ ID NO:2. Because nucleic acids with 70% identity to SEQ ID NO:3 could encode proteins with up to about 20 amino acid substitutions, and because the claims are drawn to nucleic acids that hybridize to nucleic acids comprising 16 contiguous nucleic acids of a nucleic acid encoding SEQ ID NO:4, many more than 19^{97} nucleic acids would need to be made and analyzed.

As the specification does not describe the transformation of any plant with a lipid transfer protein-encoding nucleic acids with 70% identity to SEQ ID NO:3, nucleic acids comprising at least 16 contiguous nucleotides of a nucleic acid that encodes SEQ ID NO:4, or nucleic acids that hybridize to the latter nucleic acid, undue trial and error experimentation would be required to screen through the myriad of nucleic acids encompassed by the claims and plants transformed therewith, to identify those with enhanced disease resistance, if such plants are even obtainable.

Given the claim breath, unpredictability in the art, undue experimentation, and lack of guidance in the specification as discussed above, the instant invention is not enabled.

11. Claims 15-22 and 24-26 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claim is directed to nucleic acids deposited as Patent Deposit No. PTA-2182. Since the nucleic acids are essential to the claimed invention, they must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. If the plasmids are not so obtainable or available, a deposit of microorganism containing said nucleic acids may satisfy the requirements of 35 USC 112. The specification does not disclose a repeatable process to obtain the nucleic acids and it is not apparent if the nucleic acids are readily available to the public. Thus, a deposit is required for enablement purposes.

If the deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the specific strain has been deposited under the Budapest Treaty and that the strain will be irrevocably and without restriction or condition released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein.

If the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 C.F.R. 1.801-1.809, Applicant may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;
(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;
(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the enforceable life of the patent, whichever is longer;
(d) a test of the viability of the biological material at the time of deposit (see 37 CFR 1.807); and,
(e) the deposit will be replaced if it should ever become inviable.

12. Claims 15-22 and 24-26 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to a multitude of DNA molecules that are lipid transfer protein-encoding nucleic acids with 70% identity to SEQ ID NO:3, nucleic acids comprising at least 16 contiguous nucleotides of a nucleic acid that encodes SEQ ID NO:4, or nucleic acids that hybridize to nucleic acids comprising at least 16 contiguous nucleotides of a nucleic acid that encodes SEQ ID NO:4.

In contrast, the specification only describes a coding sequence from sunflower that comprises SEQ ID NO:3. Applicant does not describe other DNA molecules encompassed by the claims, and the structural features that distinguish all such nucleic acids from other nucleic acids are not provided.

Additionally, no description is provided as to the function of the protein encoding by nucleic acids that hybridize to the latter nucleic acid or one that encodes SEQ ID NO:4.

Hence, Applicant has not, in fact, described lipid transfer protein-encoding nucleic acids with 70% identity to SEQ ID NO:3, nucleic acids comprising at least 16 contiguous nucleotides of a nucleic acid that encodes SEQ ID NO:4, or nucleic acids that hybridize to nucleic acids comprising at least 16 contiguous nucleotides of a nucleic acid that encodes SEQ ID NO:4, and the specification fails to provide an adequate written description of the claimed invention.

Therefore, given the lack of written description in the specification with regard to the structural and physical characteristics of the claimed compositions, it is not clear that Applicant was in possession of the genus claimed at the time this application was filed.

See *Univ. of California v. Eli Lilly*, 119 F.3d 1559, 43 USPQ 2d 1398 (Fed. Cir. 1997):

> The name cDNA is not in itself a written description of that DNA; it conveys no distinguishing information concerning its identity. While the example provides a process for obtaining human insulin-encoding cDNA, there is no further information in the patent pertaining to that cDNA's relevant structural or physical characteristics; in other words, it thus does not describe human insulin cDNA .... Accordingly, the specification does not provide a written description of the invention ....

and at pg 1406:

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicted, does not suffice to define the genus because it is only an indication of what the genes does, not what it is.

See *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ 2d 1016 at page 1021:

> A gene is a chemical compound, albeit a complex one, and ... conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials .... Conception does not occur unless one has a mental picture of the structure of the chemical or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by it principal biological property, *e.g.*, encoding human erythropoietin, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property.

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 15-22 and 24-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention. Dependent claims are included in all rejections.

Claims 15 and 25 are indefinite in their recitation of "the amino acid sequence encoded by a nucleotide sequence deposited as Patent Deposit No. PTA-2182" in part (d). A DNA molecule has 6 different reading frames, each comprising at least one open reading frame. It is unclear to which of the possible amino acid sequences that could be encoded by the nucleotide sequence the claim refers.

Claims 15 and 25 are indefinite in their recitation of ""stringent conditions" in part (l). It is not clear what hybridization conditions are considered stringent.

Claim 16 lacks antecedent basis for the limitation "nucleotide sequence of claim 15"and claims19 and 24 lack antecedent basis for the limitation "the nucleotide sequences of claim 15", as claim 15 is drawn to an isolated nucleic acid.

It is unclear in claim 26 if the seed is transformed with the DNA construct the plant in claim 25 was transformed with or if it was transformed with another nucleic acid, as the construct will only be transmitted to half the progeny of the plant. It is suggested that --, wherein the seed comprises the DNA construct-- be inserted after "25".

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claims 15-21 and 24-26 are rejected under 35 U.S.C. 102(b) as being anticipated by Kragh et al (WO 95/11306).

Kragh et al teach isolated nucleic acids encoding 21 contiguous nucleotides of a nucleic acid that encodes SEQ ID NO:4 (see sequence search results). Kragh et al also teach cells, seeds and plants, including sunflower, transformed with a vector comprising the nucleic acid operably linked to a plant promoter (pg 3, paragraph 2, pg 4, paragraph 3, paragraph spanning pg 9-10, and claims 8 and 13-15). Transformation of the plant comprises transforming the plant with a construct comprising the nucleic acid operably linked to a promoter and regenerating the cell into a plant (paragraph spanning pg 9-10); these are the same steps the claimed method for creating or enhancing disease resistance in a plant. Thus, Kragh et al inherently teach a method for creating or enhancing disease resistance in a plant.

17. Claim 15 is rejected under 35 U.S.C. 102(a) as being anticipated by Or et al (2000, GenBank Accession No. AF195867).

Or et al teach an isolated nucleic acid that would hybridize to SEQ ID NO:3 under "stringent conditions" (see sequence search report).

18. Claims 15-20, 22 and 24-26 are rejected under 35 U.S.C. 102(b) as being anticipated by Dixon et al (WO 98/51801).

Dixon et al teach an isolated nucleic acid that would hybridize under "stringent conditions" to SEQ ID NO:3 or nucleic acids comprising at least 16 contiguous nucleotides of a nucleic acid encoding SEQ ID NO:4 (pg 15-17). Dixon et al also teach DNA constructs and

vectors comprising the nucleic acid operably linked to the 35S promoter or an inducible promoter and methods of using them to transform tobacco and alfalfa plants to make plants with disease resistance (pg 17-19, claims 3-5 and 9-15).

Conclusion

19. No claim is allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, whose telephone number is (703) 308-5059. The examiner can normally be reached Monday through Friday, 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at (703) 306-3218. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Customer Service at (703) 308-0198.

Anne R. Kubelik, Ph.D.
March 7, 2003